Unstable mouse tumors, a mine for human cancer genes

Although mouse cancer models have been established, most genetically engineered murine cancers exhibit relatively benign cytogenetic profiles. Thus, in order to uncover genomic alterations involved in mouse cancer ontogeny, Maser and colleagues generated a murine T-cell lymphoma model with both telomere and checkpoint defects. This inherent genome instability yielded genomic alterations similar to those observed in human hematopoietic, mesenchymal, and epithelial cancers. Specifically, comparative cross-species oncogenetic studies and resequencing revealed syntenic copy number alterations in loci altered in human cancers. In addition, this analysis identified *FBXAW7* and *PTEN* as genes commonly mutated in T-cell lymphoma. Overall, these results support the use of genomically unstable murine tumor models for mining human genomic cancer alterations. (*Nature* 447:966–71, 2007)

Epidermal T-cell migration in psoriasis

Psoriasis, one of the most common T-cell-mediated chronic inflammatory diseases, involves activated epidermal T cells. Because the extracellular matrix and its associated collagen molecules form the structure of human skin, Conrad and colleagues recently explored the functional role of collagen-binding integrins on activated T cells. T cells isolated from psoriatic lesions expressed $\alpha_1\beta_1$ integrin in the epidermis but not in the dermis. These cells expressed interferon-γ but not interleukin-4, thereby identifying them as epidermal type I effector memory T cells. Blockade of the $\alpha_1\beta_1$ integrin via a monoclonal antibody in a xenotransplantation model not only inhibited T-cell migration but also abrogated development of psoriasis acanthosis and papillomatosis. These effects on psoriasis symptoms were similar to those following administration of tumor necrosis factor-α, a common psoriasis treatment. These findings indicate the relevance of the interactions between the epidermal extracellular matrix collagens and T cells in early psoriasis development. (*Nat Med* 13:836–42, 2007)

STAT3 function in hyper-IgE syndrome

Following the discovery of a mutation in the tyrosine kinase 2 gene in a patient with hyperimmunoglobulin E syndrome (HIES), Minegishi and colleagues probed genes involved in other cytokine signaling pathways. Human signal transducer and activator of transcription 3 (STAT3)—a molecule at the crossroads of a wide variety of cytokine, growth factor, and hormone response pathways—was found to harbor mutations in 8 of 15 HIES patients examined. These mutations appeared to occur *de novo*, because parental and sibling samples did not contain the mutations. The mutations were localized to the DNA-binding domain and thus impaired the DNA-binding activity of STAT3. In addition, the STAT3 mutations exhibited dominant-negative effects in a luciferase reporter assay in cultured cells coexpressing wild-type STAT3. The discovery of STAT3 mutations in HIES patients underscores the involvement of multiple cytokine pathways in the pathogenesis of HIES and offers a mechanism for early diagnosis of this immunodeficiency disease. (*Nature* 448:1058–62, 2007)

Activation of transcriptional pathways restores EB

Epidermolysis bullosa (EB), a rare disease in which epidermal integrity is lost following mechanical trauma, is commonly caused by dominantly acting mutations in keratin 5 (K5) or K14. These proteins function as components of the cytoskeletal intermediate filaments in basal keratinocytes of the epidermis. Recently, Kerns and colleagues triggered the activation of two distinct transcriptional pathways, Gli2 and Nrf2, in mice. Ectopic expression of Gli2, a terminal effector of hedgehog signaling, resulted in normal skin K14-deficient mice. These mice displayed upregulation of K17, which is highly homologous to K14. Furthermore, the use of sulforaphane to activate Nrf2 transcription yielded increased K17 expression and reduced cutaneous blistering in K14-deficient mice. The minimal overlap in these two pathways implicates the induction of K17 in basal epidermal keratinocytes as a critical factor in restoring the skin under EB conditions. Thus, the use of Nrf2 inducers such as sulforaphane may be an effective therapeutic strategy for EB patients with a mutation in the K14 locus. (*Proc Natl Acad Sci USA* 104:14460–5, 2007)

Pigment recipient in charge

Although much effort has been made toward understanding the production of pigment, little is understood about the effectors of pigment patterning. Weiner and colleagues thus investigated the role of the epithelial pigment recipient cells in determining the behavior of melanocyte pigment donor cells. In epithelial progenitor populations, expression of transgenic Foxn1, a murine gene essential for epithelial tissue development, targeted melanocytes to the epidermal cells and dictated the pigmentation pattern. Foxn1 expression induced both expression and secretion of fibroblast growth factor 2 (Fgf2), a transcription factor known to affect melanocyte behavior and pigmentation. Inhibition of Fgf2 activity in Foxn1 transgenic mice, however, rescued or normalized the pigmentation phenotype of these mice. Thus, epithelial cells that express Foxn1 signal via Fgf2 (and perhaps other signals) to melanocytes to direct the deposition of pigment. These results illuminate a pathway whereby the melanin-receiving cells dictate the pattern of melanin donation by melanocytes. (*Cell* 130:932–42, 2007)

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